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A facile synthesis of an unsymmetric benzopyranobenzopyran ring system

Ramesh M. Kanojia, Nareshkumar Jain, Jiayi Xu and Zhihua Sui*

Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 Route 202, Raritan, NJ 08869, USA

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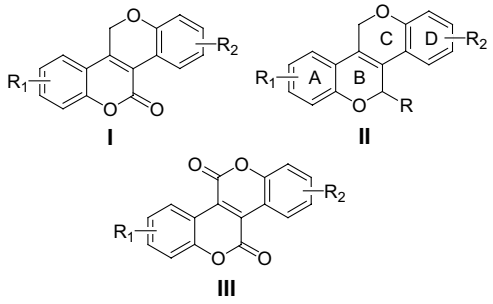
Abstract—A facile route to the synthesis of an unsymmetric benzopyranobenzopyran ring system is described. A key feature of this synthesis incorporates a tandem deprotection–cyclization strategy to construct the C-ring of the tetracyclic system.

In conjunction with our medicinal chemistry efforts to discover novel selective estrogen receptor modulators (SERMs), we chose to access the steroid-mimetic scaffold, unsymmetric bisbenzopyran **II** through the lactone precursor **I**. To facilitate our SAR studies, we looked for a synthetic method that would allow us to introduce a variety of functional groups into the A-, B-, and D-rings.



A brief survey of the literature revealed that although the synthesis of symmetrical bislactones like **III** was documented, the synthesis of an unsymmetrical system like **I** had not been well studied.[1] Using dimethoxy analog (**Ia**) as an example, we explored three literature approaches to access this key intermediate (Scheme 1).

Pechmann condensation of **a** and **b** (path A), following the Baran-Marszak conditions,[1a] gave only a trace amounts of **Ia**. Although we were able to effect isomerization of isoxindigo **c** to the symmetric bislactone **d** utilizing literature procedures (path B),[1b–d] the poor solubility of compound **d** posed a significant challenge for its desymmetrization to the desired product **I** (path B). Intramolecular Claisen type cyclization of **f** via the Box protocol[1e] (path C) also failed to deliver the desired product.

Having explored these literature approaches, we decided to access our key intermediate through coumarin **IV** (Scheme 2). The lynchpin of this strategy is the incorporation of a two-step cascade reaction sequence initiated by the deprotection of an oxygen moiety and its subsequent intramolecular nucleophilic capture of a proximally positioned electrophile to construct the C-ring. Although less likely, it is worth noting that structure **I** could be formed through electrocyclization of vinylogous *o*-quinone methide generated from **IV** upon deprotection.[1f]

Details of this cascade reaction sequence including the preparation of the precursor are outlined in Scheme 3. Modified Perkin reaction[2a–c] of a mixture of 2-hydroxyacetophenones **1** and 2,4-dimethoxyphenylacetic acid **2** in the presence of triethylamine in refluxing acetic anhydride delivered coumarin **3** in moderate to good yield. Global demethylation and deacetylation of **3a** with pyridine hydrochloride at 200 °C, per-acetylation of the tris-phenol **4a** and radical bromination of the triacetate **4b** with N-bromosuccinimide afforded the allyl bromide **5** in modest yield.

Keyword: Benzopyran.
* Corresponding author. Tel.: +1-908-704-5778; fax: +1-908-526-6469; e-mail: zsui@prdus.jnj.com

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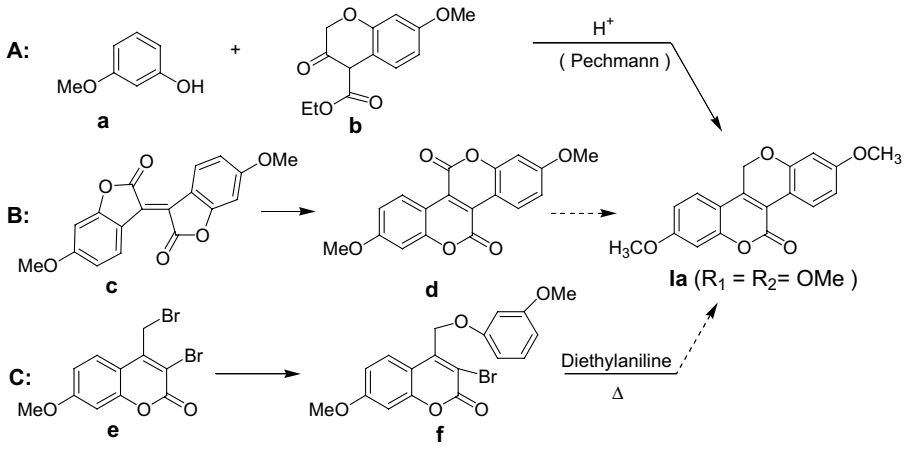
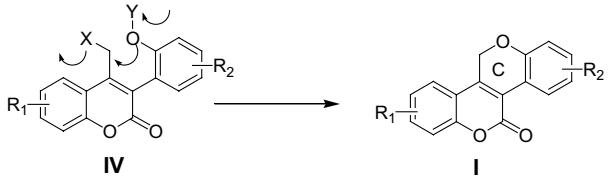


Scheme 1.

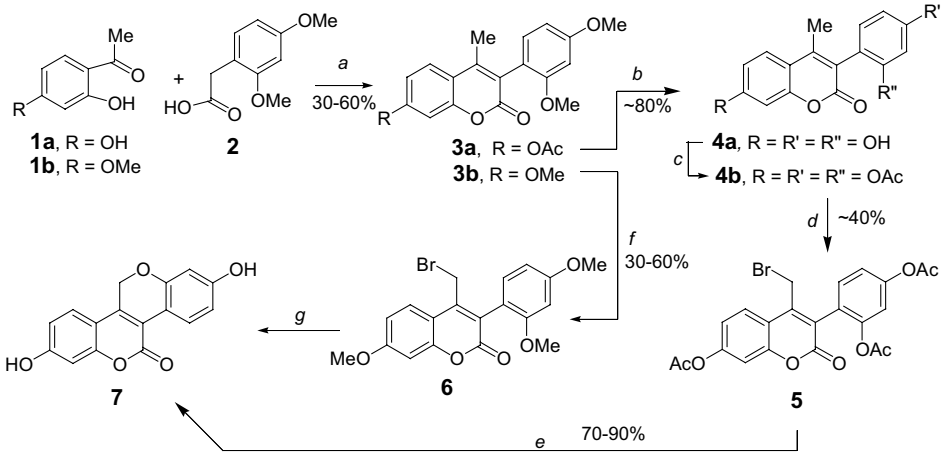


Scheme 2.

Treatment of a colorless solution of bromotriacetate **5** with K_2CO_3 in an acetone/methanol mixture at room temperature resulted in an immediate color change, indicating the rapid formation of the tetracyclic structures **7** via deacetylation of the phenyl acetate **5** followed by instantaneous displacement of the allylic bromide by the newly generated adjacent phenoxide anion to form the pyran ring C. Compound **7** was isolated by acid precipitation in high yield.[4]

We also explored the anionic bromination of **3b**, a modification that allowed us to synthesize the target lactone **7** in multi-gram quantities. Bromination of **3b** was conveniently carried out using lithium hexamethyldisilazine (LiHMDS) as a base in THF at −32 °C to generate the carbanion, which was added dropwise to a solution of NBS in THF at −78 °C to provide **6**. Demethylation of **6** was conveniently accomplished with BBr_3 in dichloromethane at room temperature. In situ treatment of the corresponding tris-phenol with aqueous NaOH solution directly resulted in the formation of **7**, which was isolated from the alkaline aqueous solution by acid precipitation.

In conclusion, we have developed a novel, convenient, and practical method to synthesize the tetracyclic benzopyranobenzopyran lactones **I**. In addition to the compounds exemplified in this paper, related analogs with various A/D ring substitution patterns including both electron-donating and electron-withdrawing groups were synthesized, and employed as pivotal intermediates in our synthesis of novel nonsteroidal SERMs.[3] The biological properties of these novel structures will be reported in future communications.



Scheme 3. Reagents and conditions: (a) Et_3N, Ac_2O/reflux; (b) pyridine, HCl/200 °C; (c) Ac_2O/pyridine; (d) NBS/benzoyl peroxide, CCl_4/hν; (e) K_2CO_3/MeOH/acetone; (f) LiHMDS/THF/−32 °C→NBS/THF/−78 °C; (g) BBr_3/DCM→NaOH/H^+.

Acknowledgements

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References and notes

1. (a) Baran-Marszak, M.; Massicot, J.; Molho, D. *Bull. Soc. Chim. Fr.* **1971**, *1*, 191–198; (b) Chatterjea, J. N.; Prasad, N. *J. Indian Chem. Soc.* **1968**, *45*(1), 35–44; (c) Nesvadba, P.; Jandke, J. WO 9952909, 1999; (d) Becker, H. D.; Lingnert, H. *J. Org. Chem.* **1982**, *47*(6), 1095–1101; (e) Box, V. G. S.; Humes, C. G. *Heterocycles* **1980**, *14*(11), 1775–1777; (f) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367–5405.
2. (a) Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 53:; (b) Perkin, W. H. *J. Chem. Soc.* **1868**, *31*, 388; (c) Bargellini, G.; Atti, R. *Accad. Lincei* **1925**, *2*, 261.
3. Kanojia, R. M.; Jain, N.; Ng, R.; Sui, Z.; Xu, J. WO 2003053977, 2003.
4. Analytical data for all the new compounds. Compound **3a**: mp 149–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, d, $J = 8.7$ Hz), 7.13–7.06 (3H, m), 6.58 (1H, d, $J = 12.13$ Hz), 6.56 (1H, s), 3.85 (3H, s), 3.76 (3H, s), 2.36 (3H, s), 2.24 (3H, s); IR (KBr) 1762, 1731, 1610, 1574, 1506 cm^{-1}; MS (CI) 355 (MH^+). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.75; H, 4.99. Compound **4a**: mp 282–283 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (1H, br s), 9.34 (2H, s), 7.62 (1H, d, $J = 8.8$ Hz), 6.81 (2H, dd, $J = 2.5$, 8.3 Hz), 6.72 (1H, d, $J = 2.2$ Hz), 6.35 (1H, d, $J = 2.1$ Hz), 6.27 (1H, dd, $J = 2.1$ Hz), 2.13 (3H, s); IR (KBr) 3454, 3264, 1673, 16160, 1562, 1509 cm^{-1}; MS (CI) 285 (MH^+), 283 (M−H). Anal. Calcd for $C_{16}H_{12}O_5/0.25H_2O$: C, 66.55; H, 4.36. Found: C, 66.63; H, 4.53. Compound **4b**: mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, $J = 8.7$ Hz), 7.26 (1H, $J = 2.3$ Hz), 7.16–7.10 (4H, m), 2.36 (3H, s), 2.32 (3H, s) 2.28 (3H, s), 2.22 (3H, s); IR (KBr) 1763, 1726, 1611, 1573, 1501 cm^{-1}; MS (CI) 411 (MH^+), 232 (M+Na). Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.23. Found: C, 64.16; H, 4.23. Compound **5**: mp 171–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, $J = 8.7$ Hz), 7.49 (1H, d, $J = 8.3$ Hz), 7.19–7.13 (4H, m), 4.40 (1H, d, $J = 10$ Hz), 4.27 (1H, d, $J = 10$ Hz), 2.38 (3H, s), 2.33 (3H, s), 2.11 (3H, s); IR (KBr) 1766, 1725, 1613, 1571, 1499, 1426, 1369, 1194 cm^{-1}; MS (CI) 488 (MH^+), 512 (M+Na). Anal. Calcd for $C_{22}H_{17}BrO_8$: C, 54.01; H, 3.50. Found: C, 54.03; H, 3.42. Compound **7**: mp >350 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (1H, br s), 9.85 (1H, br s), 8.19 (1H, d, $J = 8.0$ Hz), 7.62 (1H, d, $J = 8.1$ Hz), 6.82 (1H, d, $J = 8.2$ Hz), 6.76 (1H, s), 6.47 (1H, d, $J = -7.75$ Hz), 6.38 (1H, s), 5.33 (2H, s); IR (KBr) 3373, 1699, 1620, 1597, 1508, 1464, 1299, 1264, 1166 cm^{-1}; MS (CI) 283 (MH^+), 305 (M+Na), 321 (M+K), 281 (M−H). Anal. Calcd for $C_{16}H_{10}O_5/0.2H_2O$: C, 67.23; H, 3.67. Found: C, 67.31; H, 3.55.